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WOMBLE CARLYLE SANDRIDGE & RICE, PLLC			GOLDBERG, JEANINE ANNE	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/241,636	HEATH ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	JEANINE A. GOLDBERG	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 18 September 2008.  
 2a) This action is FINAL.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 63-93 and 101-112 is/are pending in the application.  
 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 63-93, 101-112 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | Paper No(s)/Mail Date. _____ .                                    |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>3/08</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
|   | 6) <input type="checkbox"/> Other: _____ .                        |

### **DETAILED ACTION**

1. This action is in response to the papers filed September 19, 2008. Currently, claims 63-96, 101-112 are pending.
2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 19, 2008 has been entered.
3. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.
4. Any objections and rejections not reiterated below are hereby withdrawn.
5. This action contains new grounds of rejection.

### ***New Matter***

6. Claims 63-96, 101-111 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "the lysing reagent comprises a detergent but lacks a chaotropic agent" are included. The amendment proposes that the new claim language is supported on page 3, 8 and in the examples. The response asserts

that the specification discusses the present invention uses less hazardous chemicals, including guanidinium isothiocyanate (a chaotropic agent). However, the specification does not describe or discuss “the lysing reagent comprises a detergent but lacks a chaotropic agent”. Instead the specification, on page 3, describes Boom, a prior art references which uses a high concentration chaotropic solution. Then the specification states disadvantages of this method are the use of hazardous reagents, such as guanidinium isothiocyanate and acetone. The specification never suggests that this invention overcomes these disadvantages or suggests using a lysing reagent comprises a detergent but lacks a chaotropic agent. Page 8 of the specification fails to discuss chaotropic agents or lysing agents. This description does not support the lysing reagent comprises a detergent but lacks a chaotropic agent. The concept of “the lysing reagent comprises a detergent but lacks a chaotropic agent” does not appear to be part of the originally filed invention. Therefore, “the lysing reagent comprises a detergent but lacks a chaotropic agent” constitutes new matter.

Claim 68 has been amended to require that the eluting reagent has a pH of at least about 10.5. The specification teaches, on page 9 of the specification that the eluting reagent includes a buffer to maintain the pH at least about 7, but most preferably, at least about 10. This does not support 10.5pH. The concept of “the eluting reagent has a pH of at least about 10.5” does not appear to be part of the originally filed invention. Therefore, “the eluting reagent has a pH of at least about 10.5” constitutes new matter.

Claim 110 has been added to require 140-150nM ammonium chloride. The specification teaches using 140-150mM ammonium chloride. The specification does Not support the use of 14—150nM ammonium chloride. The concept of “140-150nM ammonium chloride” does not appear to be part of the originally filed invention. Therefore, “140-150nM ammonium chloride” constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 68 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) The phrase "at least about" because the metes and bounds of the invention are not clear. As the CAFC noted, and affirmed, regarding the district court determination of this phrase in Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. (CA FC) 18 USPQ2d 1016 at page 1031 "the court held the "at least about" claims to be invalid for indefiniteness." Here too, the situation is that there is close prior art, applied as a 103 for a lower limit value, and the claim is indefinite with regard to the values encompassed.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claim 112 is rejected under 35 U.S.C. 103(a) as being unpatentable over Harvey et al. (US Pat. 5.939,259, August 1999) in view of Rudi et al. (WO 98/51693, November 19, 1998) as evidenced by Ahmed (J. of Biological Chemistry, Vol. 259, No. 7, 1994)

Harvey teaches a method and device for collecting and storing clinical samples for genetic analysis. Harvey teaches a process for characterizing DNA by isolating nucleic acids which comprises contacting a biological material with a solid support treated with a lysing reagent (i.e. a absorbent material that is impregnated with chaotropic salt); b) treating the biological material with a DNA purifying agent (i.e. water and vortex), c) purifying the DNA from the remainder (i.e. supernatant) d) analyzing the purified DNA (i.e. PCR reactions and electrophoresis)(col. 5, lines 25-55). Moreover, Harvey specifically teaches fabricating an absorbent material with a roll of 903 paper which is impregnated with guanidine thiocyanate solution having a concentration between 0.5M and 5.0 M. The paper is allowed to dry (col. 5, lines 10-22). Harvey teaches isolating DNA from fecal sources, saliva sources, and whole blood sources. Specifically, two separate squares of 903 paper are exposed to samples, one paper treated and the other paper untreated. The samples was allowed to dry and the papers was transferred to a centrifuge tube containing water and vortexed (col. 5, lines 30-35).

The paper was further transferred to a second centrifuge tube containing water and placed on a heating block at 95 degrees for 30 minutes (col. 5, lines 35-40). The supernatant from each sample was amplified and analyzed by electrophoresis on a polyacrylamide gel which were visualized by silver staining (Example 6). Moreover Harvey specifically claims a method for collecting nucleic acids from a whole blood source by contacting a whole blood source with an adsorbent material that has a chaotropic salt impregnated, allowing the source to be absorbed on the absorbent material and eluting the nucleic acids into a solution that can be used in a nucleic acid amplification process (col. 8).

Harvey does not specifically teach a method which uses an RNA digesting enzyme.

However, Rudi et al. (herein referred to as Rudi) teaches a method of solid-phase nucleic acid isolation. Rudi teaches "if it is desired to remove RNA from DNA, this may be achieved by destroying the RNA." Rudi teaches that this may be done by the addition of an RNAase or an alkali such as NaOH (page 15, lines 34-36). Rudi further teaches that any cell including prokaryotic and eukaryotic cells, mammalian and non-mammalian cells, bacteria may be used (page 4). Further samples comprising these materials may include foods, clinical and environmental samples including soil, water or food samples. Moreover, Rudi teaches analyzing the nucleic acids following isolation (page 17). Rudi discusses detecting nucleic acids using hybridization, PCR, minisequencing.

Ahmad teaches changes in denaturation of ribonuclease A by mixed denaturants including guanidinium denaturants. Ahmad teaches that the conformational free energy is not affected by the presence of low concentrations of guanidine hydrochloride which by themselves do not disrupt the structure of native ribonuclease A. Ahmad teaches combinations of denaturants and illustrates activity levels. It is not clear, as applicants suggest, that RNase is denatured and rendered unusable at low concentrations (see Figure 1, 2, 3), for example.

Therefore, it would have been *prima facie* obvious, at the time the invention was made to have modified the solid phase lysis and detection method of Harvey to include contacting the solid phase with an RNase. Harvey specifically teaches that if it is desired to remove RNA from DNA this may be done by addition of an RNAase (page 15). Therefore, the ordinary artisan would have been motivated to have removed RNA from a sample to enable detection of DNA. The ordinary artisan would have been motivated to have added a RNAase to the lysing reagent to enable the rapid detection of DNA without an additional step. The ordinary artisan would have had a reasonable expectation of success for modifying the impregnated solid support comprising a lysing reagent with an RNAase to enable a simultaneous method for lysis and removal of RNA.

Further, the ordinary artisan would have been motivated to have used any of the samples taught in the art for the efficient detection of nucleic acids. Rudi teaches many sources and samples may be used. The ordinary artisan would have been motivated to

have used any of the variety of samples taught as successful by Rudi for the express benefit of analyzing a variety of samples.

Additionally, Rudi teaches the following isolation the purified nucleic acid may be analyzed using sequencing, minisequencing, PCR, hybridization for example. The ordinary artisan would have been motivated to have taken the purified nucleic acid obtained by Harvey in view of Rudi and further analyzed the sample to obtain information regarding the nucleic acid. While Harvey teaches the nucleic acid may be used for PCR reactions, the additional analysis methods taught by Rudi would have a reasonable expectation of success to analyze the nucleic acids purified. Thus, the ordinary artisan would have been motivated to have analyzed the nucleic acids using any of the known methods depending on the desired results of the analysis.

### **Response to Arguments**

The response traverses the rejection.

The response asserts that Harvey teaches using guanidine thiocyanate solution which is a chaotropic agent. This argument has been reviewed but Claim 112 does not require that the lysing reagent not include a chaotropic agent.

Moreover, the response asserts that the pretreated solid support material has RNase adsorbed thereto and that both components have to maintain their activity when contacting the biological material. The response further asserts that one skilled in the art would appreciate that it is not possible to have a long contact between the lysing reagent and RNase without the RNase being activated when both components are in the liquid phase. This argument has been reviewed but is not persuasive. First, the

references do not state that there is "long contact between the lysing reagent and the RNase in the liquid phase." The references, namely Harvey states that the chaotropic salts are dried for about 20-30 minutes. Second, in view of the skill in the art, the skilled artisan would have separately dried the lysing reagent and the RNA digesting enzyme on the solid supports to ensure each of the elements retained their respective activity.

The response further asserts that Rudi does not teach a method for binding cells to a solid support treated with a lysing reagent and a RNA digesting enzyme because Rudi teaches binding of intact cells to the solid support. This argument has been reviewed, but is not persuasive. The teachings of Rudi have been used to illustrate that RNases may be used to remove RNA from a sample.

Thus for the reasons above and those already of record, the rejection is maintained.

9. Claim 112 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boom et al (5,234,809) in view of Shieh (US Pat. 6,054,039, April 2000) in view of Rudi et al. (WO 98/51693, November 19, 1998).

Boom teaches methods of characterizing DNA. Boom discloses a process which involved contacting the biological material that contains DNA with a solid support that had been treated with a lysing reagent (i.e. a chaotropic substance), treating the biological material with a purifying reagent, and purifying the DNA (col. 4, lines 3-59). The chaotropic substance (lysing reagent) is contacted with silica particles (solid support). The biological material is then treated with purifying reagents, and the

remainder of the biological matter is purified (washing buffer, alcohol washing solution and acetone. Additionally, the process described by Boom produces DNA which can be further used to “demonstrate NA sequences by means of an amplification method such as the PCR method....” (col.4, lines 48-50). Boom teaches that the Gus SCN (i.e. the lysis reagent ) is added to the solid support (i.e. the silica beads) prior to addition of biological material. Boom teaches silicon dioxide supports, nitrocellulose supports, latex particles (col. 5-6). As described in Boom, the DNA may be eluted from the solid support by means of an eluting reagent (col.4, line 33). Boom teaches an eluting reagent can be TE buffer, aqua bidest or PCR buffer. Boom further teaches the process where in the solid support is contained in a single vessel (col.4, lines 34-36). Boom demonstrates the use of isolating nucleic acids from a nucleic acid-containing biological material (col. 1, lines 10-20). The biological material stated includes tissues, cell cultures, blood, urine, and saliva (body fluids). The nucleic acid was taught to be examined by gel electrophoresis (col. 10, lines 13-24). This method may be used for characterizing the biological material and monitoring impurities. Yields were also taught in example A1 (col. 12, lines 46-48). Eluted DNA was treated with a restriction enzyme, electrophoresed and visualized (col. 12 65-68). Boom also teaches hybridization analysis of the isolated nucleic acids (col. 9, lines 19-21). Boom teaches a method which can “provide a process with which nucleic acid can be isolated immediately...” (col. 1, lines 64-67). Boom teaches lysis buffers containing Tris (buffer), aqua bidest, GuSCN, and EDTA (col. 6, lines 39-68).

Boom does not explicitly teach using a solid support in which the lysing reagent is bound, and unbound lysing reagent is removed prior to the contacting of the biological treatment.

However, Shieh teaches a method for lysing cells. Specifically, Shieh teaches the modification of a membrane strip to produce lysis of red blood cells that contacts it (col. 6, lines 17-20). Shieh teaches that membranes such as polymer treated glass fibers, polyamides, cellulose, polyesters may be used (col. 10, lines 42-57). Shieh teaches preparing a lysing component by treating the membranes with a lysing agent (col. 10, lines 65-67). Shieh teaches that lysing agents included Mega 8, Triton X, lauryl sulfate salts, TEA salts, sodium salt, among numerous others (col. 11, lines 1-10). Furthermore, Shieh teaches that the lysing agent may be coated onto the membrane by any method used in the art for coating solutions onto films such as dip coating an aqueous solution or dispersion of the lysing solution onto the membrane and allowing to dry (col. 11, lines 10-20). As provided in Example 1D, a cell lysing membrane was prepared (col. 12, lines 8-18). Furthermore, Shieh teaches that “this component caused lysis of whole blood when it passed across the membrane (col. 14, lines 31-33). Shieh teaches that the method and sensor may be used “on the spot: at home, in a physicians office or in a hospital room”. Shieh also teaches the sensor is low cost and disposable (col. 15, lines 55-60).

Further, Rudi et al. (herein referred to as Rudi) teaches a method of solid-phase nucleic acid isolation. Rudi teaches “if it is desired to remove RNA from DNA, this may be achieved by destroying the RNA.” Rudi teaches that this may be done by the

addition of an RNAase or an alkali such as NaOH (page 15, lines 34-36). Rudi further teaches that any cell including prokaryotic and eukaryotic cells, mammalian and non-mammalian cells, bacteria may be used (page 4). Further samples comprising these materials may include foods, clinical and environmental samples including soil, water or food samples. Moreover, Rudi teaches analyzing the nucleic acids following isolation (page 17). Rudi discusses detecting nucleic acids using hybridization, PCR, minisequencing.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Boom, which characterizes DNA using a solid support, lysing reagent and a biological material with a pre-treated membrane of Shieh. Shieh teaches that biological samples may be lysed using a pre-treated membrane such that lysis is caused when a sample is passed across the membrane. The ordinary artisan would have been motivated to have produced a solid support which was pre-treated with a lysing reagent, as taught by Shieh, for the expected benefit taught by Shieh as low cost and disposability. The ordinary artisan would also have been motivated to have prepared the pre-treated lysing membranes, of Shieh, for use in the method, of Boom, for the expected benefit of convenience. Moreover, the skilled artisan would have had a reasonable expectation of success for analyzing DNA from a solid support that was pretreated with a lysing reagent since Boom teaches a method in which all three components, a lysing reagent, solid support and nucleic acid sample, were contacted with successful results.

Further, the ordinary artisan would have been motivated to have used any of the samples taught in the art for the efficient detection of nucleic acids. Rudi teaches many sources and samples may be used. The ordinary artisan would have been motivated to have used any of the variety of samples taught as successful by Rudi for the express benefit of analyzing a variety of samples.

Additionally, Rudi teaches the following isolation the purified nucleic acid may be analyzed using sequencing, minisequencing, PCR, hybridization for example. The ordinary artisan would have been motivated to have taken the purified nucleic acid obtained by Harvey in view of Rudi and further analyzed the sample to obtain information regarding the nucleic acid. While Boom in view of Shieh teaches the nucleic acid may be used for PCR reactions, the additional analysis methods taught by Rudi would have a reasonable expectation of success to analyze the nucleic acids purified. Thus, the ordinary artisan would have been motivated to have analyzed the nucleic acids using any of the known methods depending on the desired results of the analysis.

Thus, the skilled artisan would have combined the teachings of Boom with the teachings of Shieh in further view of Rudi.

### **Response to Arguments**

The response traverses the rejection.

The response asserts that Boom teaches using guanidine thiocyanate solution which is a chaotropic agent. This argument has been reviewed but Claim 112 does not require that the lysing reagent not include a chaotropic agent.

Moreover, the response asserts that the pretreated solid support material has RNase adsorbed thereto and that both components have to maintain their activity when contacting the biological material. The response further asserts that one skilled in the art would appreciate that it is not possible to have a long contact between the lysing reagent and RNase without the RNase being activated when both components are in the liquid phase. This argument has been reviewed but is not persuasive. First, the references do not state that there is "long contact between the lysing reagent and the RNase in the liquid phase." The references, namely Sheih states that the lysing membrane is dried overnight.. Second, in view of the skill in the art, the skilled artisan would have separately dried the lysing reagent and the RNA digesting enzyme on the solid supports to ensure each of the elements retained their respective activity.

The response further asserts that Rudi does not teach a method for binding cells to a solid support treated with a lysing reagent and a RNA digesting enzyme because Rudi teaches binding of intact cells to the solid support. This argument has been reviewed, but is not persuasive. The teachings of Rudi have been used to illustrate that RNases may be used to remove RNA from a sample.

Thus for the reasons above and those already of record, the rejection is maintained.

10. Claims 63-67, 69-90, 101-109, 112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deggerdal (WO 96/18731) in view of Shieh (US Pat. 6,054,039, April

2000) or Harvey et al. (US Pat. 5.939,259, August 1999) in view of Rudi et al. (WO 98/51693, November 19, 1998).

Deggerdal teaches methods of characterizing DNA. Deggerdal discloses a “method of isolating nucleic acid from a sample, said method comprising contacting said sample with a detergent and a solid support, whereby soluble nucleic acid in said sample is bound to the support, and separating said support with bound nucleic acid from the sample” (pg 5, para 2). Deggerdal teaches that the “nucleic acid-containing sample may be contacted with the detergent and solid phase which may be added to the sample prior to, simultaneously with, or subsequently to the detergent (which functions in the method to lyse)”(pg 7, para 3, lines 22-29). The solid support was contained in a vessel (pg 26, line 18)(limitations of Claim 69). Deggerdal teaches isolation of nucleic acids and the elution of the nucleic acid by heating to 65 C for 5-10 minutes (pg 12, para 3, line 3)(limitations of claims 70). The samples may be of “any material containing nucleic acid” (pg 6, para 1, line 1-3)(limitations of claims 71-73). Deggerdal teaches a method of DNA isolation from cultured cells which indicates the number of cells used as starting material (pg 33, line 1) (limitations of claims 74-76). The purified DNA was then analyzed by PCR and visualized on agarose gel electrophoresis (pg 20, lines 29-32)(limitations of Claims 80). Detection of extra bands indicated contamination (pg 17, lines 26-27)(limitations of Claims 79). The solid support was taught to be made of “glass, silica, latex or a polymeric material” (pg 9, para 3)(limitations of claim 90). Deggerdal teaches an example where cells were lysed using DNA DIRECT Dynabeads and the lysate from each sample was further characterized

(pg 35, lines 6-35)(limitations of claim 77-78). Deggerdal teaches the lysing reagent as a detergent. This detergent may be supplied in simple aqueous solution (pg 8, line 7). Further any suitable buffer (Tris) is taught. The reagent may also include components such as enzymes, chelating agents and reducing agents (pg 8, lines 7-23).

Deggerdal does not explicitly teach using a solid support in which the lysing reagent is bound, and unbound lysing reagent is removed prior to the contacting of the biological treatment.

However, Shieh teaches a method for lysing cells. Specifically, Shieh teaches the modification of a membrane strip to produce lysis of red blood cells that contacts it (col. 6, lines 17-20). Shieh teaches that membranes such as polymer treated glass fibers, polyamides, cellulose, polyesters may be used (col. 10, lines 42-57)(limitations of Claims 33). Shieh teaches preparing a lysing component by treating the membranes with a lysing agent (col. 10, lines 65-67). Shieh teaches that lysing agents included Mega 8, Triton X, lauryl sulfate sals, TEA sals, sodium salt, among numerous others (col. 11, lines 1-10)(limitations of Claims 61-62). Furthermore, Shieh teaches that the lysing agent may be coated onto the membrane by any method used in the art for coating solutions onto films such as dip coating an aqueous solution or dispersion of the lysing solution onto the membrane and allowing to dry (col. 11, lines 10-20). As provided in Example 1D, a cell lysing membrane was prepared (col. 12, lines 8-18). Furthermore, Shieh teaches that “this component caused lysis of whole blood when it passed across the membrane (col. 14, lines 31-33). Shieh teaches that the method and

sensor may be used "on the spot: at home, in a physicians office or in a hospital room". Shieh also teaches the sensor is low cost and disposable (col. 15, lines 55-60).

Harvey teaches a method and device for collecting and storing clinical samples for genetic analysis. Harvey teaches a process for characterizing DNA by isolating nucleic acids which comprises contacting a biological material with a solid support treated with a lysing reagent (i.e. a absorbent material that is impregnated with chaotropic salt); b) treating the biological material with a DNA purifying agent (i.e. water and vortex), c) purifying the DNA from the remainder (i.e. supernatant) d) analyzing the purified DNA (i.e. PCR reactions and electrophoresis)(col. 5, lines 25-55). Moreover, Harvey specifically teaches fabricating an absorbent material with a roll of 903 paper which is impregnated with guanidine thiocyanate solution having a concentration between 0.5M and 5.0 M. The paper is allowed to dry (col. 5, lines 10-22). Harvey teaches isolating DNA from fecal sources, saliva sources, and whole blood sources. Specifically, two separate squares of 903 paper are exposed to samples, one paper treated and the other paper untreated. The samples was allowed to dry and the papers was transferred to a centrifuge tube containing water and vortexed (col. 5, lines 30-35). The paper was further transferred to a second centrifuge tube containing water and placed on a heating block at 95 degrees for 30 minutes (col. 5, lines 35-40). The supernatant from each sample was amplified and analyzed by electrophoresis on a polyacrylamide gel which were visualized by silver staining (Example 6). Moreover Harvey specifically claims a method for collecting nucleic acids from a whole blood source by contacting a whole blood source with an adsorbent material that has a

chaotropic salt impregnated, allowing the source to be absorbed on the absorbent material and eluting the nucleic acids into a solution that can be used in a nucleic acid amplification process (col. 8).

Further, Rudi et al. (herein referred to as Rudi) teaches a method of solid-phase nucleic acid isolation. Rudi teaches “if it is desired to remove RNA from DNA, this may be achieved by destroying the RNA.” Rudi teaches that this may be done by the addition of an RNAase or an alkali such as NaOH (page 15, lines 34-36)(limitations of Claim 67). Rudi further teaches that any cell including prokaryotic and eukaryotic cells, mammalian and non-mammalian cells, bacteria may be used (page 4). Further samples comprising these materials may include foods, clinical and environmental samples including soil, water or food samples (limitations of Claims 73). Moreover, Rudi teaches analyzing the nucleic acids following isolation (page 17). Rudi discusses detecting nucleic acids using hybridization, PCR, minisequencing (limitations of Clams 82, 84, 87, 88)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Deggerdal, which characterizes DNA using a solid support, lysing reagent and a biological material with the method and pre-treated membrane of Shieh or Harvey. Shieh teaches that biological samples may be lysed using a pre-treated membrane such that lysis is caused when a sample is passed across the membrane. The ordinary artisan would have been motivated to have produced a solid support which was pre-treated with a lysing reagent, as taught by Shieh or Harvey, for the expected benefit taught by Shieh

as low cost and disposability. The ordinary artisan would also have been motivated to have prepared the pre-treated lysing membranes, of Shieh, for use in the method, of Deggerdal, for the expected benefit of convenience. Moreover, the skilled artisan would have had a reasonable expectation of success for analyzing DNA from a solid support that was pretreated with a lysing reagent since Deggerdal teaches a method in which all three components, a lysing reagent, solid support and nucleic acid sample, were contacted with successful results.

Further, the ordinary artisan would have been motivated to have used any of the samples taught in the art for the efficient detection of nucleic acids. Rudi teaches many sources and samples may be used. The ordinary artisan would have been motivated to have used any of the variety of samples taught as successful by Rudi for the express benefit of analyzing a variety of samples.

Additionally, Rudi teaches the following isolation the purified nucleic acid may be analyzed using sequencing, minisequencing, PCR, hybridization for example. The ordinary artisan would have been motivated to have taken the purified nucleic acid obtained by Harvey in view of Rudi and further analyzed the sample to obtain information regarding the nucleic acid. While Deggerdal in view of Shieh teaches the nucleic acid may be used for PCR reactions, the additional analysis methods taught by Rudi would have a reasonable expectation of success to analyze the nucleic acids purified. Thus, the ordinary artisan would have been motivated to have analyzed the nucleic acids using any of the know methods depending on the desired results of the analysis.

Thus, the skilled artisan would have combined the teachings of Deggerdal with the teachings of Shieh in view of Rudi.

### **Response to Arguments**

The response traverses the rejection.

The response asserts that Harvey teaches using guanidine thiocyanate solution which is a chaotropic agent. This argument has been reviewed but Claim 112 does not require that the lysing reagent not include a chaotropic agent.

Moreover, the response asserts that the pretreated solid support material has RNase adsorbed thereto and that both components has to maintain their activity when contacting the biological material. The response further asserts that one skilled in the art would appreciate that it is not possible to have a long contact between the lysing reagent and RNase without the RNase being activated when both components are in the liquid phase. This argument has been reviewed but is not persuasive. First, the references do not state that there is "long contact between the lysing reagent and the RNase in the liquid phase." The references, namely Sheih states that the lysing membrane is dried overnight.. Second, in view of the skill in the art, the skilled artisan would have separately dried the lysing reagent and the RNA digesting enzyme on the solid supports to ensure each of the elements retained their respective activity.

The response further asserts that Rudi does not teach a method for binding cells to a solid support treated with a lysing reagent and a RNA digesting enzyme because Rudi teaches binding of intact cells to the solid support. This argument has been

reviewed, but is not persuasive. The teachings of Rudi have been used to illustrate that RNases may be used to remove RNA from a sample.

The response asserts that Deggerdal fails to teach contacting a solid support with a lysing reagent and RNA digesting enzyme. This argument has been reviewed but is not persuasive. Deggerdal teaches lysing cells for analysis. The lysis buffers of Deggerdal include SDS, TE and/or NaCl or LiCl or LiDS or SDS. It is noted that the instant specification specifically is drawn to sodium, potassium, lithium salts including dodecylsulfate (see specification page 21). Thus, the lysis reagents of the instant specification appear to be those taught by Deggerdal. The ordinary artisan would have been motivated in view of Rudi and Shieh to dry the lysing reagent on a support.

The response asserts that there is no suggestion or motivation for one of ordinary skill to combine the invention without hindsight. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). At the time the invention was made, it was more than routine to lyse cells and purify nucleic acids. It would have been a simple substitution of known elements in a predictable manner. Using RNAase would remove RNA from DNA. Drying lysing reagents on a solid support was known in the art to ease

and simplify the method of Deggerdal. This argument has been reviewed above for the reasons above and those already of record, the rejection is maintained.

11. Newly amended Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Deggerdal (WO 96/18731) in view of Shieh (US Pat. 6,054,039, April 2000) or Harvey in view of Rudi et al. (WO 98/51693, November 19, 1998) as applied to Claims above 63-67, 69-80, 82-85, 87-90, 101-109, 112.

Deggerdal in view of Shieh or Harvey and Rudy does not specifically teach the eluting reagent as specified in the claims.

However, Su teaches the elution buffer to be 5 mM Tris HCl, pH 9, and 0.5 mM EDTA (col. 10, line 17).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time of the invention was made to have modified the method of Deggerdal in view of Shieh or Harvey or Rudi to include the use of the elution buffer described in the method of Su. Claim 68 is directed to an eluting reagent having a pH of about 10.5. Here, the eluting reagent has a pH of 9 which is about 10.5. Moreover, the concentration of the buffer, base and chelating is not greater than about 20mM. The ordinary artisan would also have expected that using the elution buffer of Su in the method of Boom or Deggerdal or Harvey with the elution buffer described in Su would have provided equivalent results.

12. Claims 92-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deggerdal (WO 96/18731) in view of Shieh (US Pat. 6,054,039, April 2000) or Harvey in view of Rudi et al. (WO 98/51693, November 19, 1998) as applied to Claims above 63-67, 69-80, 82-85, 87-90, 93-96, 101-109 above and further in view of Arnold (5,599,667).

Neither Deggerdal, nor Shieh or Harvey, nor Rudi specifically teach using polyolefin as a solid support wherein polyolefin is hydrophilic and has a charge.

However, Arnold teaches polycationic solid supports that can be used purification of nucleic acids (see abstract). The polycationic support matrix is taught to include inorganic and organic materials which include glasses, polyolefins and polysaccharides (col.8, lines 55-62).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time of the invention was made to have modified the method of Deggerdal in view of Shieh or Harvey to include the solid supports of Arnold in order to make the claimed invention as a whole. The ordinary artisan would be motivated to have substituted polyolefins as a solid support in the Deggerdal or Harvey method because Arnold taught that polyolefins and glass are both suitable for DNA isolation because they meet the same “principle requirement” of “not unduly adsorbing either contaminants or nucleotide probes (col. 8, lines 61-64). Consequently Arnold shows that the silica of Boom or Deggerdal and the polyolefins of the claims are equivalent.

### **Response to Arguments**

The response traverses the rejection. The response directs the examiners attention to the discussion above. This argument has been reviewed above for the reasons above and those already of record, the rejection is maintained.

13. Claim 91 is rejected under 35 U.S.C. 103(a) as being unpatentable over Deggerdal (WO 96/18731) in view of Shieh (US Pat. 6,054,039, April 2000) in view of Rudi et al. (WO 98/51693, November 19, 1998) or Harvey et al. (US Pat. 5,939,259, August 1999) as applied to claim 92-93 above, and further in view of Hasebe (5,151,345).

Arnold teaches polycationic solid supports that can be used purification of nucleic acids (see abstract). The polycationic support matrix is taught to include inorganic and organic materials which include glasses, polyolefins and polysaccharides (col.8, lines 55-62).

However, neither Deggerdal nor Arnold specifically teaches that polyolefin is a mixture of low density polyethylene and polypropylene fibers.

However, Hasebe teaches that “a polyolefin resin is preferred, and low-density polyethylene, high-density polyethylene...or a blend thereof is preferably used”(col. 11, lines 32-39).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention was made to combine the methods of Boom or Deggerdal or Harvey and Arnold as discussed above and use the types of polyolefins taught by Hasebe. As Arnold teaches that “polyolefins” may be used in DNA isolation,

one of ordinary skill in the art would have been motivated to use a preferred polyolefin resin.

### **Response to Arguments**

The response traverses the rejection. The response directs the examiners attention to the discussion above. This argument has been reviewed above for the reasons above and those already of record, the rejection is maintained.

14. Claims 110-111 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heath (US Pat 5,973,137, February 1996) in view of Deggerdal (WO 96/18731) in view of Shieh (US Pat. 6,054,039, April 2000) in view of Rudi et al. (WO 98/51693, November 19, 1998) or Harvey et al. (US Pat. 5,939,259, August 1999).

Heath teaches a sample Preparation: White cells from three samples of human whole blood were used as a source of RNA. White cells were prepared by adding 0.3 ml whole blood to the RBC Lysis Reagent, which preferentially lyses red cells during a 10 minute incubation at room temperature. This reagent contained 144 mM ammonium chloride, 1 mM sodium bicarbonate, and 1 mM EDTA. White cells were collected by centrifuging at 15,000.times. g for 20 seconds and discarding all but 10-20 .mu.l of the supernatant fraction. The white cell pellet was vortexed for several seconds to suspend the cells in the residual supernatant fluid. Moreover, Heath teaches a Cell suspension Reagent preferably has a pH of about 7-8.5, and more preferably, about 7.5-8.0. It keeps cells intact while their cell walls are being digested by lytic enzyme. This reagent contains tris[hydroxymethyl]aminomethane (Tris), preferably, at a concentration of about

0.05-0.15 M, and more preferably, at about 0.08-0.12 M, based on the total volume of the reagent. The Cell Suspension Reagent also contains EDTA, preferably, at a concentration of about 0.05-0.15 M, and more preferably, at about 0.08-0.12 M, based on the total volume of the reagent.

Heath does not specifically teach isolating the separated cells using the lysing matrix of Claim 63.

However, as described at length above, Deggerdal, Sheieh, Harvey and Rudi teach all of the limitations of Claim 63.

Thus, the skilled artisan would have been motivated to have isolated white blood cells from whole blood or cells suspensions to permit further analysis, as taught by Heath and then lysed the white blood cells or cells from the cell suspension isolation using the lysing matrix taught by Deggerdal, Sheieh, Harvey and Rudi.

### ***Conclusion***

15. **No Claims are allowable over the prior art.**
16. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.
  - A) Harvey et al. Clinical Chem. Vol. 41, pages S108, No. 6, 1995. Harvey teaches impregnating paper with chaotropic salts and their efficiencies. DNA from blood spots collected on guanidine impregnated paper was released in high levels and contained little if any inhibitory substance for PCR. Blood collection paper treated with

this chaotrope provides a rapid and reproducible method for the preparation of DNA from dried blood spots.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

**/Jeanine Goldberg/  
Primary Examiner  
December 25, 2008**